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Serum creatinine in pregnancy: a systematic review

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Abstract**Introduction**

Standard assessment of renal function in pregnancy is by measurement of serum creatinine concentration yet normal gestational ranges have not been established. The aim of this systematic review was to define the difference in serum creatinine in healthy pregnancy compared to concentrations in non-pregnant women to facilitate identification of abnormal kidney function in pregnancy.

Methods

Medline, PubMed, Embase, Web of Science™, theses, key obstetric texts and conference proceedings were searched to July 2017. Eligible studies included quantification of serum creatinine concentration in a pregnant cohort, with either a reported local laboratory reference range or matched quantification in a non-pregnant cohort. The outcomes of interest were the mean and upper reference limits for creatinine in pregnancy, measured as a ratio of pregnant:non-pregnant values. Study heterogeneity was examined by meta-regression analysis.

Results

Forty-nine studies were identified. Data synthesis included 4421 serum creatinine values in pregnancy, weighted according to cohort size. Mean values for serum creatinine in pregnancy were 84%, 77% and 80% of non-pregnant mean values during the first, second and third trimesters respectively. The 97.5th centile (upper limit of the 95% reference range) for serum creatinine in pregnancy was 85%, 80% and 86% of the non-pregnant upper limit in sequential trimesters.

Conclusions

Based on a non-pregnant reference interval of 45-90 μ mol/L [0.51-1.02mg/dL], a serum creatinine of >77 μ mol/L [0.87mg/dL] should be considered outside the normal range for pregnancy. Future work can use this value to explore correlation of adverse pregnancy outcomes with serum creatinine concentration.

Introduction

Outside of pregnancy, glomerular filtration rates are routinely estimated from serum creatinine concentrations using standardised equations, facilitating the diagnosis of chronic kidney disease (CKD) and grading of disease severity. Such equations use demographic and clinical variables to correct for physiological factors that affect serum creatinine. However, in pregnancy, estimated glomerular filtration rates (eGFR) inconsistently underestimate renal function and should not be used.¹ eGFR calculations based on Modified Diet in Renal Disease (MDRD) calculations underestimate GFR in pregnancy by up to 41ml/min/1.73m² compared with inulin clearance.² Even in women with pre-eclampsia and contracted maternal plasma volume, eGFR remains inaccurate when derived by both MDRD and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) methods, compared with inulin and creatinine clearance.^{2,3}

Serum creatinine concentration therefore remains the only standard, single-point assessment for kidney function in pregnant populations, yet a normal range for serum creatinine in pregnancy has not been established. The upper limit (95th-97.5th centile) of creatinine concentration in healthy pregnancy varies between published cohorts. Reference range limits include values of 72µmol/L [0.81mg/dL],⁴ 80µmol/L [0.90mg/dL],⁵ 89µmol/L [1.00mg/dL]⁶ and 95µmol/L [1.07mg/dL].⁷ Such data have limited generalizability without correction for factors known to cause variance in serum creatinine including ethnicity, gestation, and the use of different creatinine assay methods. The most widely cited study of trimester-specific creatinine concentration includes only 29 healthy pregnant women.⁷ Contemporaneous

statements regarding creatinine concentration in pregnancy are largely based on expert opinion including a 'normal' range of 35-71 μ mol/L [0.40-0.80mg/dL],^{8,9} an 'average' creatinine in pregnancy of 53 μ mol/L [0.60mg/dL],¹⁰ and a recommendation that serum creatinine in pregnancy greater than 75 μ mol/L [0.85mg/dL] should raise suspicion of kidney injury.¹¹

We report here a systematic review of studies including serum creatinine concentrations in healthy pregnancy. Serum creatinine concentrations measured in pregnant cohorts were compared with either a local laboratory reference interval or with creatinine concentrations derived from a matched non-pregnant cohort. The objective of the study was to compare serum creatinine concentration in pregnancy ('exposed' cohort) with non-pregnant ('unexposed') via calculation of a ratio of pregnant:non-pregnant serum creatinine. The hypothesis of the study was that serum creatinine concentrations in pregnancy can be estimated as a proportion of matched non-pregnant values, thereby eliminating variation due to assay method and ethnicity, and allowing generation of generalisable normal reference ratios for serum creatinine concentration in pregnancy.

Methods

Data sources and searches were conducted by two authors with training in (KW, KB), and experience of (KB), systematic review methodology. Medline, PubMed and Embase were searched for first publication to July 2017. Search terms included creatinine, glomerular filtration, GFR, MDRD, Cockcroft, renal function, kidney function, biochemistry, clinical chemistry in combination with pregnan\$, trimester,

gestat\$. Specific search strategies are detailed in the supplementary material. A search of conference proceedings specific to the field of obstetrics and gynaecology, as classified by Web of Science™, was also completed. A hand search was undertaken of key English obstetric textbooks for creatinine reference ranges in pregnancy and the sources for these data were included where available. A search for academic theses relevant to pregnancy was performed via proquest.com and ethos.bl.uk.

Citations were independently screened by two authors (KW, KB) based on the title and abstract. Non-English language articles were included if a translation of the abstract into English was available. A full text review was carried out on all eligible studies, and where eligibility was uncertain from the title or abstract. If a control population was not reported, study authors were contacted to provide relevant local laboratory reference ranges for the creatinine assay used at the time their study was conducted.

Only studies reporting a local laboratory serum creatinine concentration reference interval or cohort data from a non-pregnant population, and including a measure of data spread across the cohort (standard deviation, standard error, interquartile range, centile, or normal range) were eligible. Gestational age at the time of serum creatinine measurement was required for analysis of creatinine data according to trimester. Studies that included pregnant women with kidney disease (upper reference range for creatinine in control population $>125\mu\text{mol/L}$ [1.41mg/dL]), vascular disease, diabetes and adverse pregnancy outcome including pre-eclampsia

were excluded. Any study that did not adequately describe the health of population studied was excluded, as 'normality' in the population could not be presumed. Studies were also excluded if serum creatinine concentrations were assessed in a non-pregnant cohort at less than 6 weeks post-partum.

Methodological quality of the studies was scored using the Newcastle-Ottawa scale for observational cohort studies.¹² This included measures of how representative both the pregnant and non-pregnant cohorts were of 'average' women of childbearing age in the community, the exclusion of CKD, and whether data were adequately controlled for pregnancy pathology including pre-eclampsia.

Data were extracted in duplicate by two authors (KW, KB) working independently using a proforma based on the study inclusion criteria. Author, publication year, study type (longitudinal/cross sectional), ethnicity, laboratory method for determination of serum creatinine, definition of control population, definition of normal pregnancy, gestation in weeks, and creatinine values including measures of data spread (standard deviation/error or centile) were recorded. Where cohort ethnicity was not given, black and non-black ethnicity was assigned based upon the population demographic of the country in which the study took place. Disagreements were resolved by discussion between two authors (KW, KB), with arbitration from a third author (LC).

We defined exposure as pregnancy, and gestation at sample collection was recorded. To enable comparison, creatinine measures were converted from mg/dL to $\mu\text{mol/L}$ using a conversion factor of 88.42.

A normal distribution of serum creatinine concentrations was assumed based on previously published cohort data both in non-pregnant¹³⁻¹⁶ and pregnant^{6,17} cohorts. Mean creatinine concentrations in the pregnant and non-pregnant cohorts were extracted from the raw data, or derived from the median or reference range on the assumption of a normal distribution. Similarly, creatinine reference intervals for both pregnant and non-pregnant cohorts were obtained from the available raw data or a 97.5th centile (upper limit of the 95% reference range) was calculated as the mean value + 1.96 standard deviations.

Data were divided by trimesters of pregnancy (<13 weeks, 13-26 weeks, >26 weeks gestation). Where a range of gestation was included within the data, data were allocated to the trimester for which the gestational range was most representative. If studies included more than one measure of creatinine in the same trimester, mean values for each trimester were calculated. Mean and upper reference values for creatinine concentration in pregnancy were converted to a proportion (percentage) of the equivalent value from either the non-pregnant cohort described in each study, or the mean and upper reference limit of the given local reference range. A bootstrapping method (described below) was then used to provide a combined estimate for each trimester.

Statistical analysis was performed using Stata version 14.2. We used the calculation of the I^2 statistic^{18,19} to test for heterogeneity in the pregnant:non-pregnant ratio between studies. Where heterogeneity was found, meta-regression was used to assess whether the differences between studies was due to the use of cross-sectional data, year of publication, the specific exclusion of renal disease, Jaffe and enzymatic methods of creatinine measurement, or black ethnicity. This was done by separate linear regression of each variable, in each trimester, with impact on the pregnant:non-pregnant creatinine ratio measured as a coefficient value. Year of publication was analysed as a continuous measure and by conversion to decade. Analytic weights were defined by Stata.

The calculation of pregnant:non-pregnant creatinine ratios meant that standard error measurements were not available, with no accepted method to estimate this quantity from summary data. The complexity of determining the variance and distribution of a ratio value meant we were unable to use most standard meta-analysis techniques including DerSimonian and Laird estimates of the combined effect, Forest plots, and an assessment of publication bias.²⁰ Data from the included studies were therefore synthesised using a bootstrapping technique. This involved repeat sampling (10,000 repetitions) with each study acting as a single observation. Bootstrapping was informed by the assessment of heterogeneity and the results of the meta-regression. Heterogeneity between studies was high ($I^2 > 99\%$). The inclusion of studies using a reference range as the non-pregnant comparator revealed an irreconcilable heterogeneity of data which prevented meaningful synthesis. Heterogeneity was however reduced ($I^2 = 12.3$) when the pregnant:non

pregnant ratio was examined using studies with a large (>100 women) non-pregnant cohort. Meta-regression revealed the importance of pregnant cohort size. The bootstrapping technique therefore included all studies with a non-pregnant cohort, weighted according to the product of the geometric mean of pregnant and non-pregnant cohort size. Bias-corrected confidence intervals were generated using an automatic algorithm, which estimates and corrects for bias in the sampling process.²¹

This systematic review was registered on the PROSPERO database with registration number CRD42017068446.

Results

Electronic searching identified 3297 unique citations including 11 sources identified by hand searching of textbooks. Of the 3267 available sources, we excluded 3033 sources on the basis of title and abstract review. The majority of excluded papers were studies of urinary creatinine concentration in pregnancy usually performed as part of a urinary protein:creatinine ratio in pre-eclampsia, and did not include serum creatinine measurement. Studies of amniotic, fetal or neonatal creatinine measurement were also excluded. A further 185 sources were excluded after full-text review (Figure 1). Four studies were included after contacting the authors to provide local laboratory reference ranges at the time of their study .

Forty-nine studies were included in the analysis. Study characteristics including reference details, ethnicity, study type, sample size, trimester specific creatinine

measurements, creatinine assay method, assessment of normal pregnancy and the Newcastle-Ottawa assessment of study quality are reported in Table 1.

Median pregnant cohort sizes were 40, 40 and 35 in the first, second and third trimesters respectively (interquartile range 17-67). Of the 49 included studies, only nine had creatinine concentrations from more than 100 women within the same trimester. Detail regarding the specific exclusion of renal disease was made in 22 studies.

Non-pregnant control cohorts were the 'unexposed' comparator in 39 studies. The median non-pregnant cohort size was 19 women (interquartile range 13-52). Only three studies included more than 100 non-pregnant women in the control cohort. Serum creatinine in pregnancy was compared to a laboratory reference interval in 10 studies. No details were available regarding how these laboratory reference intervals had been derived and whether they were specific to a female population.

Most studies had limited reporting of creatinine assay methods. Creatinine was quantified using the Jaffe reaction in 24 studies and by a kinetic enzymatic reaction in 11 studies. Assay method was not available for 14 studies. Inter-assay precision was reported in only 10 studies. No studies documented whether creatinine assay methods were traceable to an isotope dilution mass spectrometry (IDMS) reference, according to current recommendation.²²

Study quality was variable. In 19 of the 49 studies 'normal' pregnancy was confirmed after completion of the pregnancy, with exclusion of data from women who experienced an abnormal pregnancy. However quality scores ranged from 4-9 on the Newcastle-Ottawa scale based on selection, comparability and outcome. Based on previously described thresholds for quality assessment,²³ only 11 of the 49 studies were classified as 'good' quality for this systematic review.

Meta-regression demonstrated that the size of the pregnant cohort had a significant impact on the pregnant:non-pregnant creatinine ratio across all three trimesters. The use of cross-sectional data, year and decade of publication, the specific exclusion of renal disease, creatinine assay method, and black ethnicity showed no significant effect on the ratio result (Table 2).

Data synthesis included all studies which had a matched pregnant control cohort as the non-pregnant comparator. This included 816 creatinine values (19 studies) from the first trimester, 1183 creatinine values (22 studies) from the second trimester, and 2422 creatinine values (30 studies) from the third trimester. Mean values for serum creatinine in pregnancy were 84% (95% confidence interval 76%-90%), 77% (72%-83%), and 80% (77%-84%) of mean values outside of pregnancy during the first, second and third trimesters respectively. Using the 97.5th centile (upper limit of the 95% reference range), serum creatinine in pregnancy was 85% (76%-93%), 80% (73%-89%), and 86% (83%-89%) of the upper reference limit for non-pregnant females in sequential trimesters (Table 3, Figure 2).

Discussion

Data synthesis from this systematic review creates a mean and upper reference limit for serum creatinine in pregnancy, compared to non-pregnant values. Mean serum creatinine in pregnancy is 77-84% of mean values outside of pregnancy, and the reference limit for serum creatinine is 80-86% of that in non-pregnant women. Based on a normal female range for serum creatinine of 45-90 μ mol/L [0.51-1.02mg/dL],²⁴ this equates to mean serum creatinine values of 56 μ mol/L [0.63mg/dL], 52 μ mol/L [0.59mg/dL] and 54 μ mol/L [0.61mg/dL] in sequential trimesters, whilst serum creatinine values greater than 76 μ mol/L [0.86mg/dL] in the first trimester, 72 μ mol/L [0.81mg/dL] in the second trimester, and 77 μ mol/L [0.87mg/dL] in the third trimester should be considered to be outside the upper limit of normal for pregnancy. A serum creatinine greater than 77 μ mol/L [0.87mg/dL] in pregnancy should raise the possibility of either acute kidney injury (AKI), or undiagnosed CKD predating the pregnancy.

As far as we are aware, this is the only study published to date that attempts to offer a value for serum creatinine in pregnancy which is generalizable and not limited to a specific population or creatinine assay technique. The strength of this study is that, through the use of a ratio of pregnant to non-pregnant values, it provides a synthesis of published creatinine data from multiple normal pregnant cohorts, across different ethnicities and assay techniques. Previous reports of creatinine concentration according to gestation are limited by small numbers of women, diverse methodology and insufficient information about disease states in 'normal women'.

The main limitation of this study is in the amount of heterogeneity in the included data. This is likely to be due to a combination of both study design and clinical factors. The complexity of generating standard deviation or standard error values for a ratio value²⁰ means that the precision of each study is not considered in the meta-analysis. In addition, creatinine data are summarised as single value for each trimester which may fail to adequately represent the true variation in serum creatinine for individual pregnant women, including a progressive physiological adaption to both early pregnancy and parturition.²⁵⁻²⁸

Heterogeneity was reduced when the ratio of pregnant:non-pregnant creatinine used a matched non-pregnant cohort, compared to ratios generated from laboratory reference intervals. This is likely due to quantification in a control population being performed over the same time period as the samples taken during pregnancy, conferring less analytical variance and better reproducibility of values.²⁹ In contrast, heterogeneity when using a laboratory reference range as the non-pregnant comparator may have arisen due to baseline differences between the reference and pregnant cohorts including gender, age and ethnicity; although there was insufficient information on the generation of the reference intervals in the included studies to allow assessment of this.

Meta-regression showed no significant difference in the pregnant:non-pregnant creatinine ratio related to the use of alkaline picrate (Jaffe) or enzymatic assay method. This suggests that either the two techniques are affected by pregnancy

equally, or that differences between assay techniques are insignificant relative to the effect of pregnancy on serum creatinine concentration. However, dichotomisation by assay technique may be overly simplistic. This review includes internationally diverse studies, performed over a 34-year period. Although the majority of studies used a Jaffe method, this is known to lack standardisation, resulting in significant methodological variation, which is not measurable in this study.³⁰ Confirmation of the findings of this systematic review using IDMS traceable creatinine assay methods²² is warranted.

The results of this study concur with the known physiological changes of pregnancy; namely a fall in serum creatinine due to gestational hyperfiltration resulting in a 50% increase in creatinine clearance by the second trimester,²⁶⁻²⁸ followed by a decrease in creatinine clearance during the third trimester²⁵ leading to an increase in serum creatinine concentration towards term. This study suggests that the normal range for creatinine in pregnancy is either comparable to,⁴ or lower⁵⁻⁷ than that derived from other published cohorts, which are limited by assay method, ethnic differences in creatinine, and small cohort sizes.

The synthesis of data in this study generated a mean value and upper reference range limit for creatinine in pregnancy as a relative proportion of a matched non-pregnant cohort. In practice, clinicians have access to a laboratory reference range for creatinine, rather than a matched control value. For example, at the authors' institution (Guy's and St. Thomas NHS Foundation Trust), the female-specific reference interval for serum creatinine is 45-90 μ mol/L [0.51-1.02mg/dL]. This is

derived from 269 healthy, Red Cross blood donors.²⁴ Although gender specific, this reference interval is not specific for women of child-bearing age as the reference population is aged 18-70 years. However, the use of this reference interval to derive values for child-bearing age women can be justified on the basis that an increased prevalence of silent chronic kidney disease with age is potentially counterbalanced by a simultaneous age-related decline in creatinine synthesis,³¹ with minimal effect on absolute serum creatinine values. Indeed, serum creatinine values have been shown to be stable in female, white European populations between the ages of 20 and 70 years.¹⁴ However, the generation of an upper limit for serum creatinine in pregnancy through conversion of a local reference range will always be subject to the limitations under which that reference range was generated, and whether that reference interval is appropriately matched for gender and ethnicity.

Acute kidney injury occurs most commonly during pregnancy in the third trimester, predominantly due to the development of hypertensive disorders and puerperal pathologies including sepsis and haemorrhage.³²⁻³⁵ Diagnostic criteria for AKI do not exist in pregnancy and up to 40% of pregnancy-associated AKI may be missed by clinicians in the UK.³⁶ In this study, the upper reference limit for serum creatinine in the third trimester is based on data from 30 studies including 2422 pregnant women. Based on a non-pregnant upper limit for creatinine of 90 μ mol/L [1.02mg/dL],²⁴ a new serum creatinine of >77 μ mol/L [0.87mg/dL] should trigger investigation for underlying AKI.

This study generated a mean and upper reference limit for creatinine in pregnancy, as a percentage of that outside of pregnancy. In the absence of both a valid measure of eGFR and practical measure of true GFR in pregnancy, the assessment of renal function in pregnant women remains limited to serum creatinine despite confounders, insensitivity, and inter-assay variability. However, the use of creatinine thresholds of 85%, 80% and 86% of the upper limit of the non-pregnant reference range for the first, second and third trimesters respectively, represents a new and clinically relevant diagnostic parameter, which is potentially generalisable across different cohorts and creatinine assays methods.

A clinically relevant reference interval distinguishes physiology from pathology. The clinical utility of the pathological threshold suggested by this systematic review now requires prospective studies which correlate a creatinine in pregnancy that is >86% of the upper limit for non-pregnant females with adverse maternal and/or neonatal outcomes. Whether a similar percentage change in serum creatinine in pregnancy is seen in women with chronic kidney disease remains unknown, although a failure of serum creatinine to fall in the first trimester of pregnancy is hypothesised to represent a failure of the renal system to adapt in pregnancy and is used anecdotally as a poor prognostic indicator.³⁷ Future research is required into patterns of serum creatinine change in women with chronic kidney disease who do and do not develop adverse pregnancy outcomes.

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Supplementary Material

Supplementary material: Electronic Search Strategy (Word document .docx)

Supplementary information is available at KI Report's website

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Author	Year	Country/ Ethnicity	Longitudinal or cross- sectional	Control			Trimester 1			Trimester 2			Trimester 3			Creatinine assay method	Assessment of pregnancy normality*	Normal pregnancy outcome confirmed	Newcastle- Ottawa grade
				n	Mean Cr	ULN	n	Mean Cr	ULN	n	Mean Cr	ULN	n	Mean Cr	ULN				
Afolabi³⁸	2011	Nigeria	C	15	58 [0.65]	80 [0.90]				9	61 [0.69]	93 [1.05]	3	57 [0.64]	104 [1.18]	Jaffe	1		6
Akbari³⁹	2005	Canada	C	13	74 [0.84]	86 [0.97]				68	52 [0.59]	69 [0.78]	68	54 [0.61]	78 [0.88]	Not stated	2		7
Al Kuran⁴⁰	2012	Jordan	L	LRR	70 [0.79]	96 [1.10]	797	67 [0.76]	97 [1.10]	797	64 [0.72]	100 [1.13]	797	72 [0.81]	132 [1.4]	Jaffe	2		6
Babay⁴¹	2005	Saudi Arabia	C	40	58 [0.66]	71 [0.80]	54	56 [0.63]	75 [0.85]	53	57 [0.64]	81 [0.92]	50	52 [0.59]	70 [0.79]	Not stated	3	Yes	8
Babu⁴²	2013	India	C	LRR	71 [0.80]	78 [0.88]							25	52 [0.59]	70 [0.79]	Not stated	3		4
Chapman²⁸	1998	WE:AC=10:1	L	13	71 [0.80]	88 [1.00]	10	65 [0.74]	77 [0.87]	8	53 [0.60]	73 [0.83]	8	49 [0.55]	68 [0.77]	Jaffe	3		8
Collins⁴³	1981	Canada	C	65	71 [0.80]	88 [1.00]							350	53 [0.60]	71 [0.80]	Jaffe	1		6
Davison²⁵	1980	UK	L	10	69 [0.78]	104 [1.18]							10	60 [0.68]	104 [1.18]	Enzymatic	3	Yes	9
Davison²⁶	1981	UK	L	9	72 [0.81]	85 [0.96]	9	64 [0.72]	77 [0.87]	9	57 [0.64]	69 [0.78]				Enzymatic	3	Yes ⁺	8
Djordjevic⁴⁴	2004	Serbia- Montenegro	L	30	61 [0.69]	83 [0.94]	30	65 [0.74]	91 [1.03]							Not stated	1		7
Duvekot⁴⁵	1995	Netherlands	L	10	56 [0.63]	63 [0.71]	10	53 [0.60]	68 [0.77]							Not stated	1	Yes	6
Fasshauser⁴⁶	2008a	Germany	C	LRR ^{\$}	76 [0.86]	104 [1.18]							20	55 [0.62]	79 [0.89]	Not stated	1		5
Fasshauser⁴⁷	2008b	Germany	C	LRR ^{\$}	76 [0.86]	104 [1.18]							20	54 [0.61]	79 [0.89]	Not stated	3		5
de Flamingh⁴⁸	1984	South Africa	C	16	74 [0.84]	88 [1.00]	10	61 [0.69]	75 [0.85]	10	55 [0.62]	71 [0.80]	40	54 [0.61]	93 [1.05]	Not stated	3		4

Girling⁶	2000	47% WE, 21% AC, 10% Med	C	LRR ^{\$}	88 [1.00]	120 [1.36]	20	68 [0.77]	84 [0.95]	271	63 [0.71]	125 [1.41]	68	54 [0.61]	97 [1.10]	Jaffe	3	6	
Guo⁴⁹	2012	China	L	LRR ^{\$}	89 [1.00]	115 [1.30]				96	42 [0.48]	52 [0.59]	96	54 [0.61]	70 [0.79]	Jaffe	3	4	
Hanna⁵⁰	2009	Iraq	C	40	84 [0.95]	121 [1.37]	40	83 [0.94]	118 [1.33]	40	75 [0.85]	94 [1.06]	40	54 [0.61]	92 [1.04]	Jaffe	3	7	
Heguilén⁵¹	2007	Argentina	C	8	82 [0.93]	102 [1.15]				5	66 [0.75]	88 [1.00]				Not stated	3	4	
Iqbal⁵²	2003	Pakistan	C	26	72 [0.81]	89	18	65 [0.74]	95	22	70 [0.79]	94	23	69 [0.78]	94	Jaffe	1	6	
Järnfelt-Samsioe⁵³Λ	1985	Sweden	C	LRR	80 [0.90]	110 [1.24]				37	68 [0.77]	94 [1.06]	34	66 [0.75]	94 [1.06]	Not stated	2	Yes ⁺	4
Jaing⁵⁴	2013	Italy	C	19	53 [0.70]	66 [0.75]							29	42 [0.48]	58 [0.66]	Not stated	1	Yes	7
Kametas⁵⁵#	2003	Peru	C	13-15	55-63 [0.62- 0.71]	68-80 [0.77- 0.90]				77- 80	47-56 [0.53- 0.63]	58-74 [0.66- 0.83]				Jaffe	2	Yes	6
Klajnbard⁵⁶	2010	Denmark (WE)	L	LRR	70 [0.79]	90 [1.02]				532	58 [0.66]	73 [0.83]	358	62 [0.70]	84 [0.95]	Enzymatic	2	Yes	7
Knopp⁵⁷	1985	USA (WE)	C	77	67 [0.76]	88 [1.00]							546	51 [0.58]	78 [0.88]	Jaffe	1		5
Koetje¹	2011	Netherlands (WE)	C	44	69 [0.78]	91 [1.03]	44	58 [0.66]	74 [0.84]							Jaffe	2		4
Kristensen¹⁷	2007a	Sweden	C	58	65 [0.74]	82 [0.93]	94	53 [0.60]	70 [0.79]	107	51 [0.58]	64 [0.72]	88	54 [0.61]	70 [0.79]	Enzymatic	3	Yes ⁺	6
Kristensen⁵⁸	2007b	Sweden	C	58	65 [0.74]	82 [0.93]							218	53 [0.60]	68 [0.77]	Enzymatic	3	Yes	6
Lain⁵⁹	2005	USA	L	63	50 [0.57]	92 [1.04]	63	51 [0.58]	92 [1.04]	63	44 [0.50]	99 [1.12]	63	50 [0.57]	92 [1.04]	Enzymatic	2	Yes	9
Larsson⁴	2008	Sweden	L	51	67 [0.76]	86 [0.97]	50	49 [0.55]	62 [0.70]	51	46 [0.52]	62 [0.70]	52	47 [0.53]	72 [0.81]	Jaffe	2	Yes ⁺	6

Lockitch ⁷	1993	Majority WE	L	121	73 [0.83]	94 [1.06]	29	52 [0.59]	77 [0.87]	29	50 [0.57]	73 [0.83]	29	56 [0.63]	87 [0.98]	Enzymatic	2	Yes	6
Lohsiriwat ⁶⁰	2008	Thailand	L	26	72 [0.82]	90				26				64 [0.72]	84	Jaffe	3	Yes	9
Mahendru ⁶¹	2014	91% WE	L	54	68 [0.77]	88 [1.00]	54	53 [0.60]	69 [0.78]							Not stated	2	Yes	7
Majewska ⁶²	2010	Poland	L	40	72 [0.81]	94 [1.06]	40	50 [0.56]	63 [0.72]	40	46 [0.52]	60 [0.68]	40	52 [0.59]	75 [0.85]	Not stated	3	Yes	8
Makuyana ⁶³	2002	Zimbabwe	C	LRR	78 [0.88]	121 [1.37]				72				52 [0.59]	70 [0.79]	Jaffe	3		6
Matteucci ⁶⁴	1997	Italy	L	18	82 [0.93]	102 [1.15]	18	64 [0.72]	82 [0.93]	18	62 [0.70]	78 [0.88]	18	65 [0.74]	77 [0.87]	Jaffe	2	Yes	4
Milman ⁶⁵	2007	Denmark	L	164	75 [0.85]	96 [1.09]				394	55 [0.62]	71 [0.80]	521	58 [0.66]	81 [0.92]	Jaffe	2	Yes	7
Milne ⁶⁶	2002	UK (WE)	L	11	65 [0.74]	95 [1.07]							11	75 [0.85]	78 [0.88]	Not stated	3	Yes	9
Miri-Dashe ⁶⁷	2014	Nigeria	C	127	79 [0.89]	118 [1.33]	43 [±]	46 [0.52]	68 [0.77]	43 [±]	46 [0.52]	59 [0.67]	43 [±]	65 [0.74]	94 [1.06]	Enzymatic	1		6
Ogueh ⁶⁸	2011	UK	L	13	88 [1.00]	107 [1.21]	12	78 [0.88]	96 [1.09]	13	77 [0.87]	105 [1.19]	12	74 [0.84]	106 [1.20]	Jaffe	1	Yes	8
Pahl ⁶⁹	2001	USA	C	15	67 [0.76]	83 [0.94]				16	64 [0.72]	76 [0.86]				Enzymatic	3		7
Roberts ²⁷	1996	UK (WE)	L	11	74 [0.84]	88 [1.00]				16	54 [0.61]	66 [0.74]	11	53 [0.60]	63 [0.71]	Jaffe	3	Yes	9
Saxena ⁷⁰	2012	USA	L	12	71 [0.8]	101 [1.14]				12	53 [0.60]	77 [0.87]	12	62 [0.70]	80 [0.91]	Jaffe	1	Yes	8
Schoenmaker ⁷¹	2013	Gambia	C	10	59 [0.67]	89 [1.00]							10	74 [0.84]	68 [0.77]	Enzymatic	1		5
Siddiqui ⁷²	1993	Pakistan	C	30	69 [0.79]	88 [1.00]							35	49 [0.64]	58 [0.76]	Jaffe	3		7
Strevens ⁷³	2002	Sweden	C	12	61 [0.69]	83 [0.94]							14	48 [0.54]	66 [0.75]	Enzymatic	3		6

Van Buul ⁷⁴	1995	Netherlands	L	LRR	70 [0.79]	90 [1.02]	66	59 [0.67]	70 [0.79]	66	59 [0.68]	70 [0.79]	66	59 [0.67]	75 [0.85]	Jaffe	3	Yes	8
Vural ⁷⁵	1998	Turkey	C	15	63 [0.72]	95 [1.07]				20				61 [0.69]	73 [0.83]	Jaffe	2		4
de Weerd ^{76§}	2003	Netherlands	L	96	70 [0.79]		188	62 [0.70]								Jaffe	2	Yes ⁺	6
Weissberg ⁷⁷	1991	Israel	C	9	77 [0.87]	92 [1.04]				32				61 [0.69]	71 [0.81]	Jaffe	1		5

Table 1: Study characteristics. Creatinine values are given as $\mu\text{mol/L}$ [mg/dL]. Cr= creatinine, ULN= upper limit of normal, LRR= laboratory reference range, WE=white European, AC=Afro-Caribbean, Med=Mediterranean *Assessment of pregnancy normality: 1=limited data, 2=exclusion of comorbidity associated with abnormal renal function eg pre-eclampsia, diabetes, vascular disease, 3=specific exclusion of renal disease, ⁺but not excluded from study data, [§]=provided by study author/centre or available from an alternative source and appropriate for date of study, [^]= women with emesis excluded from extracted data, [#]= includes 2 study cohorts at different altitude, [±]=Total 131 pregnant women, distribution between trimesters not recorded, [§]=mean creatinine data only, upper limit data not derived from interquartile range.

Variable	Coefficient (95% confidence interval)	p-value
Pregnant cohort size*	0.026 (0.002 to 0.049)	0.03
Cross sectional data	0.064 (-0.082 to 0.211)	0.38
Year of publication	-0.003 (-0.013 to 0.007)	0.52
Decade of publication (compared to 2010-2017):		
• 1980	0.218 (-0.333 to 0.377)	0.90
• 1990	-0.044 (-0.300 to 0.211)	0.72
• 2000	0.059 (-0.096 to 0.214)	0.44
Exclusion of renal disease	0.094 (-0.198 to 0.386)	0.52
Enzymatic method for creatinine (compared to Jaffe method)	-0.069 (-0.286 to 0.319)	0.91
Black ethnicity	-0.266 (-0.592 to 0.061)	0.11

Table 2: Meta-regression showing impact of each variable on the pregnant:non-pregnant serum creatinine ratio in the second trimester. The coefficient is a measure of the difference in the pregnant:non-pregnant ratio between studies that can be attributed to that variable. [*=per 100 women]

Trimester	1 st	2 nd	3 rd
Number of included studies	19 [#]	22	30
Number of creatinine measures in pregnancy	816 [#]	1183	2422
Mean creatinine in pregnancy as % of non-pregnant mean value (95% CI)	84% (76-90)	77% (72-83)	80% (77-84)
Example mean creatinine*	56µmol/L [0.63mg/dL]	52µmol/L [0.59mg/dL]	54µmol/L [0.61mg/dL]
Upper limit creatinine as % of non-pregnant upper limit based on a 95% reference range (95% CI)	85% (76-93)	80% (73-89)	86% (83-89)
Example upper limit creatinine*	76µmol/L [0.86mg/dL]	72µmol/L [0.81mg/dL]	77µmol/L [0.87mg/dL]

Table 3: Creatinine in pregnancy as a percentage of non-pregnant value according to trimester

*Example creatinine values are based on a typical value for non-pregnant females of 67.5µmol/L [0.76mg/dL], and an upper limit of 90µmol/L [1.02mg/dL].¹²

[#]19 studies (816 creatinine measures) inform the mean value and 18 studies (628 creatinine measures) inform the upper limit. CI=confidence interval.

Figure legends

Figure 1: Flow diagram of the identification process for eligible studies

Figure 2: Pregnant:non-pregnant ratio for the upper limit of serum creatinine. Squares represent the point estimate of the ratio for each study, sized according to the study weight (geometric mean product of pregnant and non-pregnant sample size). Confidence intervals are not available due to the complexity of determining the precision of a ratio value. Overall is the summary value and 95% confidence interval generated by the bootstrapping technique for each trimester.

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Figure 1: Flow diagram of the identification process for eligible studies





